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Association between Baseline Fetal Hemoglobin Levels and Incidence of Severe Vaso-Occlusive Pain Episodes in Children with Sickle Cell Anemia

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Abstract

The ameliorating effect of high fetal hemoglobin (HbF) levels on the incidence of pain episodes in sickle cell anemia (SCA) is well known; however, this relationship in children with SCA is less clearly established. We tested the hypothesis that higher HbF levels in children with SCA are associated with decreased incidence of severe pain episodes, defined as an event requiring hospitalization. Based on a uniform definition of severe pain in two cohorts, a meta-analysis was performed using data from the Silent Infarct Transfusion (SIT) Trial (n= 456) and the Cooperative Study of Sickle Cell Disease (CSSCD) (n=764). Baseline HbF levels were associated with the incidence of severe pain (P-value=0.02). Hospitalization for pain is a viable SCA endo-phenotype for future study.

Keywords

Sickle cell anemia; fetal hemoglobin; vaso-occlusive pain

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INTRODUCTION

The clinical manifestations of sickle cell anemia (SCA) begin early in life and continue with an increased incidence of adverse events coincident with the physiologic decline in fetal hemoglobin (HbF) [1, 2]. Vaso-occlusive pain episodes are one of the predominant clinical features associated with SCA and show large inter-patient variability in their frequency and intensity [3]. The association between the incidence of pain and HbF levels was initially established with a seminal study from the Cooperative Study of Sickle Cell Disease (CSSCD) that included both children and adults with SCA [3]. Subsequently, hydroxyurea was introduced as a therapeutic agent, largely because of its potential to increase HbF levels [4, 5]. The initial hydroxyurea phase III clinical trial in adults with SCD (Multicenter Study of Hydroxyurea, MSH) demonstrated that hydroxyurea, when compared to placebo, dramatically decreased the rate of hospitalization for pain episodes [5]. Later, the most rigorous randomized, double-blind, placebo-controlled trial of hydroxyurea in children with SCD, the BABY HUG Trial, replicated the results of the MSH trial, demonstrating that administration of hydroxyurea decreased the rate of painful episodes, including dactylitis [6].

In the past, literature has established that increased HbF levels not only correlate with less severe complications of SCA, such as vaso-occlusive pain [3], acute chest syndrome (ACS) [7] etc., but also with improved survival [8]. Although, increased HbF levels have been shown to decrease SCA related complications in adults, its added value in children and adolescents are much less well-established. Specifically, young children with SCA and generally higher HbF levels have clinical manifestations such as dactylitis, splenic sequestration, and silent cerebral infarcts (SCI) at a greater rate than older children with lower HbF levels. These events occur when HbF levels are close to their maximum levels, rather than at minimum levels. Furthermore, in a recent study among children with SCA in Saudia Arabia, HbF level was not associated with vaso-occlusive episodes [9]. Taken together, these data suggest that the influence of HbF levels in vaso-occlusive episodes may be less in children with SCA.

No consistent objective parameter can be used to assess vaso-occlusive pain episodes. The challenge of measuring pain is further complicated by the location of where the pain episode is treated (at home or the hospital). Given that most pain episodes occur at home and are treated with oral opioids and not in the hospital with intravenous opioids [10], an accurate assessment of all mild and severe vaso-occlusive pain events would require a daily pain diary, an activity that would be prohibitive for large studies. For these reasons, we elected to pursue the most severe phenotype of vaso-occlusive pain episodes (i.e. vaso-occlusive episodes that required hospitalization) to evaluate the relationship between pain events and HbF levels. Based on compelling evidence to target increasing HbF levels as a modulator of severe SCA, we tested the hypothesis that HbF levels in children (5 to 15 yrs) with SCA are associated with the incidence of severe pain episodes requiring hospitalization. Additionally, we set out to determine the utility of a readily discernible vaso-occlusive pain phenotype from electronic medical records (defined as an event that required hospitalization) that could be used across multiple studies.

METHODS

The Silent Infarct Transfusion (SIT) Trial is an international, multi-center clinical study funded by the National Institute of Neurological Disorders and Stroke (NINDS) (http://sitstudy.wustl.edu/) [11]. Details of the study design are given elsewhere [11]. The CSSCD was a multi-institutional prospective longitudinal study of SCD funded by the National Heart, Lung, and Blood Institute (NHLBI) [12]. Both studies were approved by the IRB of each participating institution and conducted in accordance with institutional guidelines.

A vaso-occlusive pain episode in the SIT Trial was defined as an event that required hospitalization, was treated with opioids and occurred in the three years prior to signing the informed consent; all patients with pain associated with ACS or pneumonia were excluded, whereas dactylitis was included as a pain event only if it was severe enough to result in admission and treatment with opioids. After excluding non-African-American ancestry and first-degree relatives, a total of 456 SIT Trial participants were identified whose %HbF levels were measured in a central laboratory. In the CSSCD, pain episodes were defined prospectively. Unlike previous CSSCD pain analysis, where the definition of pain included a vaso-occlusive event that lasted at least two hours and resulted in a physician visit [3], we restricted the definition of pain to include only those requiring hospitalization, to match the SIT Trial definition. Similarly, because the SIT Trial only enrolled patients ≥5 and ≤15 years of age and collected data on pain events occurred in the three years prior to enrollment, participants from the CSSCD were restricted to ≥2 and ≤12 years of age (n=764), to approximate the age and length of follow-up for the SIT Trial. The pain definition in the CSSCD excluded dactylitis, ACS, and right upper quadrant pain. In both cohorts, analyses were performed using a multivariable Poisson regression (with correction for over-dispersion) and adjusting for age, sex (males=1, females=0), and %hematocrit levels. See Supplemental Material for other details.

RESULTS AND DISCUSSION

In the SIT Trial and the pediatric component of the CSSCD cohort, the average age of patients with SCA was 8.87 and 6.18 years of age, respectively, **Table I**. In both pediatric cohorts, we determined whether a unit change in the covariates of interest (age, sex, hematocrit and HbF levels) was associated with a change in the incidence of severe pain episodes (defined as hospitalization). Each analyzed covariate is on a different scale of units; therefore, for the uniform comparison, the standardized beta coefficients were referred to as the effect on vaso-occlusive pain. In the SIT Trial, an increase in age (P-value <0.0001) and hematocrit levels (P-value <0.0001) were strongly associated with incidence of severe pain, and HbF levels showed marginal significance (P-value=0.07), **Table II.** We used the same definition as in the SIT Trial to characterize pain episodes in the CSSCD cohort and did not observe a significant association of HbF levels with the incidence of severe pain episodes (P-value=0.15), whereas, increase in age (P-value=0.0016) and hematocrit levels (P-value=0.019) were associated with pain levels, **Table II**.

We performed a fixed-effect meta-analysis and combined the results from the two cohorts with identical phenotypes for severe pain over a similar interval of time, approximately 3

years. The meta-analysis revealed that HbF levels were significantly associated with severe pain (P-value=0.02) (**Table II and Figure 1**) and suggested, if sex (males), age and hematocrit levels were held constant, an increase in 1 unit of HbF would correspond to an average decrease of 5% in the frequency of vaso-occlusive pain episodes in SCA children (**Table II**). However, when sex (males), age and hematocrit were held constant, and baseline levels of HbF were divided into four quartiles, the patients with upper HbF quartile (n=310) showed the average small decrease of 7% in incidence rate of pain episodes compared to the patients in the lowest lower quartile % (n=298) (data not shown).

In this study, we provided supporting evidence that HbF levels were associated with severe vaso-occlusive pain episodes that required hospitalization in children with SCA. Although HbF levels showed significance only in the meta-analysis, the observed effects of HbF on vaso-occlusive pain events were in the same direction and had similar size in both the SIT Trial and CSSCD cohorts. These data strongly suggest that HbF levels have a definitive, but small impact on the incidence rate of pain in children with SCA. Similar to previous vaso-occlusive pain studies [13, 14], we have validated that counting inpatient admissions for pain replicates the counting of pain episodes occurring predominantly in outpatient settings. These findings validate the use of vaso-occlusive pain resulting in hospitalization as a phenotype that can easily be obtained via an electronic medical record review. Definitions of pain used in previous studies of this issue have been variable and have included self-reported pain [10], pain that lasted for two hours and required a physician visit [3], and pain that required hospitalization [14]. Each definition has unique attributes; however, in the case of self-reported pain or pain that requires a visit to a physician office, the challenges of ongoing data entry, coupled with validation of each event make these definitions challenging to use in a multi-center study. In contrast, vaso-occlusive pain events that require hospitalization are readily accessible through electronic medical records, easily amenable to quality control, and represent a quantifiable metric for pain.

Even though we confirmed the association of HbF levels with the incidence rate of pain requiring hospitalization in children with SCA (aged between ≥ 2 and ≤ 15 yrs), we recognize that using single time point data for HbF levels is a potential limitation of our study. However, at the ages of the individuals with SCA studied, the HbF would not be expected to vary significantly over a three year period. This is consistent with the observation that, while the age of the SIT Trial and CSSCD participants in this study varied significantly, there were no significant differences in the HbF levels between the two groups. Other weaknesses include the fact that, for the SIT Trial, painful episodes were collected retrospectively, and medical records from other hospitals may not have been included; however, this would not have been true for the CSSCD. The effects of sex, hematocrit and age on the incidence of pain were similar for the SIT Trial and CSSCD multi-variable equations, Table II. These results strongly suggest that any potential bias from not including other hospitalizations for pain events in the SIT Trial is minimal.

In summary, the primary result of this study confirms that higher HbF levels are associated with fewer severe vaso-occlusive pain events in children with SCA. As higher HbF levels correlate with fewer pain events and regulation of HbF levels is under the influence of genetic factors, we propose that the discovery of the factors responsible for genetic variation

of severe vaso-occlusive pain is feasible, and these investigations are much more likely to be successful if translational research teams harmonize SCA pain phenotypes and pool their results. Based on our findings, hospitalization for pain is a viable SCA endo-phenotype worthy of further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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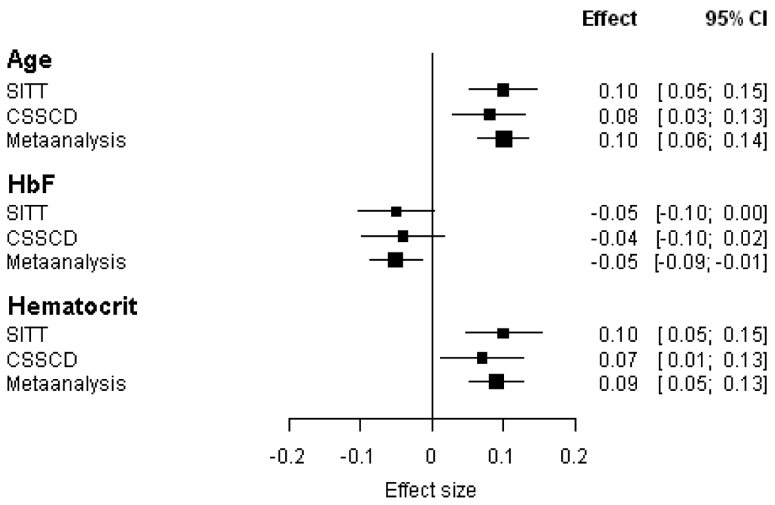

Figure 1. Forest plot showing the effects of age, hematocrit and HbF levels on severe vaso-occlusive pain using fixed effect meta-analysis

The figure shows the study-specific and the combined effect estimates with 95% confidence intervals (CI) for both the SIT Trial and CSSCD cohorts. In meta-analysis the combined effect sizes were estimates using fixed-effect model.

Table I

Demographic and clinical characteristics of participants evaluated in the SIT Trial and pediatric component of the CSSCD cohort

Characteristic	SIT Trial† (n=456)	CSSCD‡ (n=764)	P-value*
Sex, n (%)			
Males	242 (53.1)	396 (51.8)	0.67
Age (in yrs), mean ± SD	8.87 ± 2.57	6.18 ± 2.90	<0.001
Follow-up (in yrs), mean ± SD	3.00 ± 0.0	2.9 ± 0.34	<0.001
Pain rate (events/patient year)	0.58 ± 0.78	0.48 ± 0.87	0.03
Hematocrit (%), mean ± SD	23.48 ± 3.34	23.79 ± 3.11	0.10
Hemoglobin (g/dl), mean ± SD	8.19 ± 1.08	8.16 ± 0.96	0.55
Fetal Hemoglobin (%), mean ± SD	8.71 ± 5.52	9.16 ± 5.83	0.17
Reticulocytes (%), mean ± SD	12.12 ± 5.27	12.92 ± 5.47	0.01
White Blood Cells, 10^9/L	12.73 ± 5.06	12.72 ± 3.01	0.98

The laboratory assessments for both the cohorts were measured at baseline.

† The Silent Infarct Transfusion (SIT) Trial is a multi-center clinical study designed to determine the efficacy of blood transfusion therapy for prevention of recurrent silent cerebral infarction in individuals with sickle cell anemia. In this study, the age range was 2-15 yrs at enrollment; pain events were defined as those occurring 3 yrs retrospectively; the youngest patient enrolled is 5 yrs of age.

‡ The Cooperative Study of Sickle Cell Disease (CSSCD) was initiated to determine the natural history of sickle cell disease (SCD) from birth to death, in order to identify those factors contributing to the morbidity and mortality of the disease. In this study, the age range at enrollment was 2-12 yrs; pain events were defined as those occurring 3 yrs prospectively; therefore, the age range in which they developed pain is 2-15 yrs.

* P-values are based on comparison using student's t-test, but the significance for the follow-up (in yrs) is based on Wilcoxon rank sum test, with continuity correction.

Table II

Multivariable analysis of severe vaso-occlusive pain episodes in the SIT Trial and pediatric component of the CSSCD cohort

Covariates	SIT Trial † (age ≥ 2 and ≤ 15 yrs) (n=456)				CSSCD‡ (age ≥ 2 and ≤ 15 yrs) (n=764)				Meta-analysis			
	Effect	SE	95% CI	P-value*	Effect	SE	95% CI	P-value*	Effect	SE	95% CI	P-value*
Age	0.10	0.024	(0.05, 0.15)	< 0.0001	0.08	0.026	(0.03, 0.13)	0.0016	0.10	0.018	(0.06, 0.14)	< 0.0001
Sex	−0.02	0.025	(−0.06, 0.03)	0.54	−0.01	0.025	(−0.06, 0.04)	0.67	−0.01	0.018	(−0.05, 0.02)	0.46
Hematocrit	0.10	0.027	(0.05, 0.15)	< 0.0001	0.07	0.029	(0.01, 0.13)	0.019	0.09	0.019	(0.05, 0.13)	< 0.0001
HbF	−0.05	0.027	(−0.10, 0.01)	0.07	−0.04	0.029	(−0.10, 0.02)	0.15	−0.05	0.019	(−0.09, −0.01)	0.02

‡In the CSSCD, some participants did not have full 3 yrs of follow-up; therefore, log follow-up time was included as an "offset" in the model. Vaso-occlusive pain episodes were modeled using a multivariable Poisson regression adjusted for age, sex (males=1, females=0), hematocrit and fetal hemoglobin levels. The effect sizes shown for sex correspond to males. Effect sizes shown for all the covariates are standardized beta coefficients and refer to the frequency of vaso-occulusive pain episodes

†The Silent Infarct Transfusion (SIT) Trial is a multi-center clinical study designed to determine the efficacy of blood transfusion therapy for prevention of recurrent silent cerebral infarction in individuals with sickle cell anemia. In this study, vaso-occlusive pain episodes were defined as the number of hospitalizations for pain, retrospectively over 3 yrs of follow-up (age range 2-15 yrs); the youngest patient enrolled is 5 yrs of age.

‡The Cooperative Study of Sickle Cell Disease (CSSCD) was initiated to determine the natural history of sickle cell disease (SCD) from birth to death in order to identify those factors contributing to the morbidity and mortality of the disease. Vaso-occlusive pain episodes were defined as number of hospitalizations occurring 3 yrs prospectively; over prospective 3 yrs (age range at enrollment 2-12 yrs); therefore, the age range in which they developed pain is 2-15 yrs).

*Significance for the associations are shown as two-tailed p-values